38. (Amended) A therapeutic agent in a dosage form and concentration suitable for treating or [preventing] inhibiting atherosclerosis in a mammal in need of such treatment, said agent being effective to inhibit interaction between P-selectin and a ligand of P-selectin.

Add the following new claim:

39. (New) The method of claim 1 wherein said agent further inhibits interaction between E-selectin and a ligand of E-selectin.

REMARKS

The Office Action

Claims 1-13, 19, 20 and 23-38 are under examination. Claims 1-13, 19, 20, 23-31 and 35-38 are rejected under 35 U.S.C. §112, first paragraph. Claims 28-31 are rejected under 35 U.S.C. §112, second paragraph. Claims 1-13, 19, 20 and 23-38 are rejected under 35 U.S.C. §103. Claims 1-12, 19, 20 and 26-38 are rejected under 35 U.S.C. §103. Claims 1, 28-31 and 38 have been amended. Claim 39 has been added.

35 U.S.C. §112, first paragraph

Claims 1-13, 19, 20, 23-31 and 35-38 have been rejected under 35 U.S.C. §112, first paragraph. The Examiner states that the disclosure "is enabling only for claims which do not read on prevention of atherosclerosis." Applicants believe that the

disclosure is enabling for claims which read on prevention of atherosclerosis. However, in order to advance the prosecution, applicants have amended claims 1, 28-31 and 38, so as to replace "preventing" with "inhibiting," and so as to replace "prevent" with "inhibit," as suggested by the Examiner.

Since claims 2-13, 19, 20, 23-27 and 35-17 depend from and contain all the limitations of amended claim 1, these amendments also address the rejection of these claims.

35 U.S.C. §112, second paragraph

Claims 28-31 have been rejected under 35 U.S.C. §112, second paragraph. The Examiner states that the claims are "indefinite as to intended meaning of 'partially prevent.'" Applicants believe that "partially prevent" is not indefinite. However, in order to advance the prosecution, applicants have amended claims 28-31 so as to replace "prevent" with "inhibit," as suggested by the Examiner.

35 U.S.C. §103

(a) Claims 1-13, 19, 20 and 23-38 have been rejected under 35 U.S.C. §103 as being unpatentable over Kogan et al., Rao et al., or Seekamp et al., in view of Ross. The rejection of claims 1-13, 19, 20 and 23-38 is respectfully traversed.

Section 103 does not obviate the invention with respect to applicants' claims. Applicants' invention has unique advantages and is different from the cited prior art. The cited art, singly or in combination, neither suggests the desirability of these advantages nor a way of achieving them. An obviousness rejection

is not proper where the prior art contains no suggestion of the invention.

Independent claim 1 as amended recites a method for treating or inhibiting atherosclerosis in a mammal comprising providing an agent for inhibiting interaction between P-selectin and a ligand of P-selectin, and administering the agent to a mammal in need of such treatment to cause such inhibition to occur.

Independent claim 38 as amended recites a therapeutic agent in a dosage form and concentration suitable for treating or inhibiting atherosclerosis in a mammal in need of such treatment, the agent being effective to inhibit interaction between P-selectin and a ligand of P-selectin.

Kogan et al. teaches a method for treating "ARDS, Crohn's disease, septic shock, traumatic shock, multi-organ failure, autoimmune diseases, asthma, inflammatory bowel disease, psoriasis, rheumatoid arthritis, reperfusion injury that occurs following heart attacks, and strokes and organ transplants," by administering certain specified compounds. See column 4, lines 14-23. Kogan et al. does not teach or suggest to a person of ordinary skill in the art the idea of treating or inhibiting atherosclerosis by providing an agent for inhibiting interaction between P-selectin and a ligand of P-selectin. Indeed, the recital of such a long list of diseases that can be treated in Kogan et al.'s invention, makes the absence of specifying "atherosclerosis" even more glaring.

Rao et al. teaches a method of treating an animal for inflammation, comprising administering anthraquinone and anthracene derivatives. See, e.g., column 4, lines 31-34. Rao

et al. does not teach or suggest to a person of ordinary skill in the art the idea of treating or inhibiting atherosclerosis by providing an agent for inhibiting interaction between P-selectin and a ligand of P-selectin. Inflammation and atherosclerosis are very different diseases. As stated in applicants' specification at page 6, line 33 through page 7, line 3: "It is known that P-selectin is involved in cellular responses to inflammation resulting from injury or infection. This invention demonstrates that P-selectin can also be involved in the formation of atherosclerotic lesions." Further, Rao et al. notes that:

> Formulations of the present invention might also be administered to prevent the undesirable aftereffects of tissue damage resulting from heart attacks. When a heart attack occurs and the patient has been revived, such as by the application of anticoagulants or thrombolytic (e.g., tPA), the endothelial lining where a clot was formed has often suffered damage. When the antithrombotic has removed the clot, the damaged tissue beneath the clot and other damaged tissue in the endothelial lining which has been deprived of oxygen become activated. The activated cells such as endothelial cells then synthesize the selectin receptors within hours of the cells being damaged. The receptors are extended into the blood vessels where they adhere to ligand molecules on the surface of white blood cells. Large numbers of white blood cells are quickly captured and brought into the tissue surrounding the area of activated endothelial cells, resulting in inflammation, swelling and necrosis which thereby decreases the likelihood of survival of the patient. (Emphasis added). (Column 10, line 64 through Column 11, line 15).

Again, Rao's invention is for treating inflammation, and is in sharp contrast to atherosclerosis. Compare to applicants'

specification at pages 1-2:

> It is believed that the earliest type of atherosclerotic lesion is formed by binding of monocytes and T lymphocytes ($CD4^+$ and $CD8^+$) to the surfaces of endothelial cells in the lumen of the artery wall. These migrating cells proceed to penetrate beneath the arterial surface. The monocytes become macrophages, accumulate lipid, and become foam cells. These cells, together with the T lymphocytes, form a lesion called the fatty streak. The fatty streak subsequently develops into a fibrofatty intermediate lesion which is composed predominantly of layers of smooth muscle cells together with lipid-filled macrophages and T cells. These lesions in turn develop into complex occlusive lesions called fibrous plaques. The fibrous plaques can increase in size by projecting into the arterial lumen, and may thereby impede the flow of blood. Sudden death from myocardial infarctions can result from ruptures in the fibrous cap of the plaque, causing hemorrhage into the plaque, thrombosis and occlusion of the artery. (Emphasis added).

Thus, in contrast to the Examiner's conclusion, Rao et al.'s teachings are not for treating "a highly related cardiovascular disorder" to atherosclerosis.

Seekamp et al. teaches the use of sialyl $Lewis^x$ to define selectin requirements in local (crural muscle) and remote (lung) injury following ischemia/reperfusion of rat hind limbs. Seekamp et al. does not teach or suggest treating or inhibiting atherosclerosis. Nor does Seekamp et al. teach the treatment of a "highly related cardiovascular disorder" to atherosclerosis.

Ross is a review article which discusses atherosclerosis in general. The Examiner states:

> Ross provides a description of the role of platelets in atherosclerosis, and suggests that inhibition of platelets is a means of treating atherosclerosis .... Ross also describes the various steps of atherosclerosis....

Ross, however, does not teach or suggest treating or inhibiting atherosclerosis by providing an agent for inhibiting interaction between P-selectin and a ligand of P-selectin.

The Examiner further states:

> The teaching of Ross had specifically disclosed the link between atherosclerosis and cell adhesion molecules such as selectins, thereby providing one of ordinary skill in the art with a reasonable expectation of successful treatment of atherosclerosis by this method.

The Examiner has not pointed to any specific statements in Ross which support such a disclosure or conclusion, and applicants do not believe that Ross has such a teaching.

No combination of the cited references suggests a method for treating or inhibiting atherosclerosis by providing an agent for inhibiting interaction between P-selectin and a ligand of P-selectin, nor does any combination suggest the advantages that are inherent in applicants' invention. In the absence of any such suggestion in the cited references, it cannot be said that the invention would be obvious.

Even if one made the combination suggested by the Examiner, it does not meet the limitations recited in the claims under rejection. Ross does not supply those elements of the claims absent from Kogan, Rao or Seekamp. Accordingly, the combination

does not result in the advantages of the claimed invention.

Moreover, even if (for arguments' sake only) the combination of references did make applicants' invention "obvious," it would only be "obvious to try," and not "obvious to succeed," as is required. "Obvious to try" is not sufficient for a finding of obviousness under §103. See, e.g., In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988), in which the Federal Circuit states:

> It is true that this court and its predecessors have repeatedly emphasized that "obvious to try" is not the standard under §103....
>
> The admonition that "obvious to try" is not the standard under §103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices.... In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. (Emphasis added).

The Examiner further states that the specific identity of the ligand (claim 7) is not patentably distinct. Applicants' believe that different agents may be effective with different P-selectin ligands, and that different ligands will be more advantageous for inhibition purposes than others. Therefore, the identity of the ligands listed in claim 7 are patentably distinct from any ligands cited in the prior art.

In sum, claims 1-13, 19, 20 and 23-38 are felt to distinguish patentably over Kogan, Rao or Seekamp in view of Ross.

(b) Claims 1-12, 19, 20 and 26-38 have been rejected under 35 U.S.C. §103 as being unpatentable over Rohrer et al. in view of De-Ambrosi, if necessary further in view of Ross. The rejection of claims 1-12, 19, 20 and 26-38 is respectfully traversed.

Rohrer et al. teaches that heparin is an inhibitor of platelet degranulation. Rohrer et al. does not teach or suggest treating or inhibiting atherosclerosis by providing an agent for inhibiting interaction between P-selectin and a ligand for P-selectin.

De-Ambrosi teaches a method for treating atherosclerosis by administering certain epoxy-heparide polysaccharides which have been prepared by a specific process. De-Ambrosi does not teach or suggest treating or inhibiting atherosclerosis by providing an agent for inhibiting interaction between P-selectin and a ligand for P-selectin.

Ross is a review article which discusses atherosclerosis in general. The Examiner states:

> Ross provides a description of the role of platelets in atherosclerosis, and suggests that inhibition of platelets is a means of treating atherosclerosis .... Ross also describes the various steps of atherosclerosis....

Ross, however, does not teach or suggest treating or inhibiting atherosclerosis by providing an agent for inhibiting interaction between P-selectin and a ligand of P-selectin.

The Examiner further states:

The teaching of Ross had specifically disclosed the

> link between atherosclerosis and cell adhesion molecules such as selectins, thereby providing one of ordinary skill in the art with a reasonable expectation of successful treatment of atherosclerosis by this method.

The Examiner has not pointed to any specific statements in Ross which support such a disclosure or conclusion, and applicants do not believe that Ross has such a teaching.

No combination of the cited references suggests a method for treating or inhibiting atherosclerosis by providing an agent for inhibiting interaction between P-selectin and a ligand of P-selectin, nor does any combination suggest the advantages that are inherent in applicants' invention. In the absence of any such suggestion in the cited references, it cannot be said that the invention would be obvious.

Even if one made the combination suggested by the Examiner, it does not meet the limitations recited in the claims under rejection. Neither De-Ambrosi or Ross supplies those elements of the claims absent from Rohrer. Accordingly, the combination does not result in the advantages of the claimed invention.

Moreover, even if (for arguments' sake only) the combination of references made applicants' invention "obvious," it would only be "obvious to try," and not "obvious to succeed," as is required. And, "obvious to try" is not sufficient for a finding of obviousness under §103. See, e.g., In re O'Farrell, 853 F.2d 894, 903 (Fed. Cir. 1988), in which the Federal Circuit states:

> It is true that this court and its predecessors have repeatedly emphasized that "obvious to try" is not the standard under §103....
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> The admonition that "obvious to try" is not the

> standard under §103 has been directed mainly at two kinds of error. In some cases, what would have been "obvious to try" would have been to vary all parameters or try each of numerous possible choices.... In others, what was "obvious to try" was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it. (Emphasis added).

The Examiner further states that the specific identity of the ligand (claim 7) is not patentably distinct. Applicants' believe that different agents may be effective with different P-selectin ligands, and that different ligands will be more advantageous for inhibition purposes than others. Therefore, the identity of the ligands listed in claim 7 are patentably distinct from any ligands cited in the prior art.

The Examiner also states that the source of the agent (claim 25) is not patentably distinct. The source of the agent (e.g., snake venom or plant extract), however, can identify a unique agent, and therefore is patentably distinct from any given agent cited in the prior art.

In sum, claims 1-12, 19, 20 and 26-38 are felt to distinguish patentably over Rohrer in view of De-Ambrosi, or in view of Ross.

It is noted that claim 39 has been added. No new matter has been added. Support for this claim is found in the specification at page 12, lines 21-26.

Summary

In view of the above, it is respectfully submitted that the claims are in condition for allowance and such action is requested.

If the Examiner will not allow this application upon receipt and consideration of this amendment, it is respectfully requested that the Examiner call applicants' undersigned counsel or the attorney of record prior to final action in order to discuss the issues and advance the prosecution of the application.

Respectfully submitted,

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